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Long term effects and clinical outcome of low-dose azithromycin in young patients with cystic fibrosis: a multicenter, randomized, double-blind, placebo-controlled trial

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Aims : Macrolides are known to display immuno-modulatory effects that have been reported to be beneficial in various chronic pulmonary inflammatory diseases. The aim of the study was to document whether long term use of azithromycin may be associated with respiratory benefits in young patients with cystic fibrosis (CF).
Methods : The study was a multi-center (18 CF centers in France), randomised, double blind placebo-controlled trial, conducted from October 2001 to June 2003. The criteria for enrolment were a diagnosis of CF, age older than 6 yr, and forced expiratory volume in 1 second (FEV1) of 40% or more. The azithromycin (Az) group received either 250 mg (weight <40kg) or 500 mg (weight >40kg) for 1 year.
Results : 72 patients (mean age : 10.9 ± 3.4 yr) were randomly assigned treatment and analysed. Only 15 patients were infected with Pseudomonas aeruginosa. The % predicted FEV1 at start of trial in the Az and placebo (Pl) groups was respectively 88.7 ± 25.7% and 85.6 ± 18.1%. The relative change in FEV1 at the end of the trial was not significantly different between the 2 groups (Az:-5±18% vs Pl:-1±14%). By contrast, the average number of pulmonary exacerbations was significantly reduced in the Az group ($p<0.002$) regardless the infectious status, as well as the number of additional antibiotic courses ($p<0.002$). No adverse events were reported.
Conclusions : Results obtained in this first report of long term trial with low doses azithromycine in young patients with CF demonstrate a benefit on lung disease expression, even prior colonization with Pseudomonas aeruginosa.
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Long-term azithromycin (AZM) in Cystic Fibrosis (CF) children infected with Pseudomonas aeruginosa (Pa)

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The aim of this study is to describe retrospectively the long-term effect of AZM on pulmonary function and sputum microbiology in CF patients infected with Pa.
Methods: The case files of CF children who took AZM for at least one year were reviewed. 33 patients infected with Pa received AZM on a regular basis, 3 times a week. All patients attended the outpatient clinic every 2 months and sputum samples or throat swabs for microbiological analysis were obtained. During AZM treatment chronic infection was defined by the presence of 3 positive cultures in one year. Patients > 6 y performed lung function tests once a year. Student t-test was applied for statistical analysis of %FEV1; p value < 0.05 considered significant. Results were presented as median (range) values.
Results: 33 patients were included. Median age at start of treatment was 6.7 y (1.2-14.8). The duration of treatment varied from 17 to 53 months. 15 patients performed lung function tests. Median % FEV1 before treatment was 78 (58-121). 4 different treatment periods were analysed: 5-15mo, 16-21mo, 28–34mo and 35-49mo. The %FEV1changes were, respectively, 75.5(61-102), 85(69-96), 86,5(48-107), 95.5(38-107). No significant differences were observed. 23 patients (69%) showed no alteration in the microbiologic profile during AZM. New pathogens were identified in 6 patients (18%): S aureus (3 patients); MRSA (1patient), Alc. xylosidans (1patient) and M. tuberculosis (1patient). In 4 patients (12.1%) the following previously identified pathogens were no longer present: Pa and S aureus (2 patients), Pa (2 patients).
Conclusions: Historical controls suggest that a decline in FEV1 would be more likely expected if conventional treatment had been given. The fact that no significant changes in FEV1 were seen during this long-term treatment suggests that AZM may be responsible for the maintenance of lung function in CF patients. No specific pattern could be identified in the microbiological profiles during AZM treatment. A controlled prospective trial is needed to confirm these findings.

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Evaluation of the observance of inhaled Tobramycin (Tobi®), by comparing the duration of dispensary delivery with the medical prescription in cystic fibrosis

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Time spent for nebulizations made compliance as a major task in CF management. On the other hand, long term b.i.d nebulization of Tobi® was recommended in pseudomonas aeruginosa (PA) chronic colonization. To evaluate the relevance of long term prescription regarding a realistic prescription, we assess compliance by comparing the dispensary Tobi® delivery with the medical prescription.
Method: In France, Tobi® was delivered to the patient only from hospital Pharmacy. Then, Tobi® dispensary delivery (DD) was prospectively and exhaustively registered by using a drug management retrocession software (Gest'cess®, Symphony online ltd) and compared with the corresponding medical prescriptions (MP). DD represented the effective and MP the recommended administration of the drug and were expressed in month of treatment. A ratio DD/MP=1 defined compliant (C) and DD/MP<1 non compliant patients (NC). Treatment arrest for adverse effect were excluded.
Result: From 1999 to 2003, 42 patients (23 children,19 adults) were included (median age 14.5 years) and 26 were C and 16 NC. Median MP duration was longer than that in DD 8[6-16] vs. 6 [6-12] mths ($p<0.001$). A strong inverse correlation was found between DD/MP ratio and the recommended duration of Tobi® (Rho=-0.697, $p<0.001$). DD/MP was dependent on the indication ($p=0.002$) but not age. Multivariate analysis showed that compliance was only dependent on MP ($p<0.001$). A treatment > 6 months decreased dramatically the compliance (OR=19 [3.4-105.7].
Conclusion: Our results suggest that a realistic prescription should not exceed a 6 months Tobi® course. This study confirmed the high frequency of non observance in inhaled tobramycin treatment, by using an objective method. We demonstrate that chemist by using a drug management software provided a useful compliance index to the practitioner.

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Lung function, serum immunoglobulin G subclasses and serum/sputum IL-8 levels in CF patients

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Aim: This study was undertaken to define a correlation between lung function, serum immunoglobuline G (IgG) subclasses and serum/sputum IL-8 levels in patients with CF.
Material and methods: We examined 17 clinical stable CF patients aged 12-30. All patients were chronic infected with Pseudomonas aeruginosa. FEV1 and VC were measured. Total IgG, IgG1, IgG2, IgG3, IgG4 (mg/dl) in serum and serum/sputum IL-8 levels (pg/dl) were determined.
Results: Mean FEV1 and VC were 57,2±23,5% and 66,4±25,9% predicted respectively. Mean total IgG levels were 1510±556,9, IgG1 9,552±2,5l, IgG2 4,8±2,04, IgG3 1,058±0,6 and IgG4 1,787±0,725. Mean serum and sputum IL-8 levels were 19,9±3,4 and 557,1±374,5.
We found significant correlation between elevated total serum IgG levels and decreased FEV1 (p=0,006). High levels of IgG2 were significantly correlated with decreased FEV1 (p=0,021) and VC (p=0,042) and significant correlation between IgG2 and sputum IL-8 (p=008) levels was observed. There was significant correlation between elevated levels of IgG4 and increased FEV1 (p=0,013) and VC (p=0,023). Significant inverse correlation between IgG4 levels and serum (p=0,003) and sputum (p=0,002) IL-8 levels were observed. We found significant inverse correlation between FEV1 and sputum IL-8 levels (p=0,024) and between VC and serum/sputum IL-8 levels (p<0,001).
Conclusions: Elevated IgG2 levels could be a useful marker of inflammatory process in CF patients chronic infected with Pseudomonas aeruginosa and high levels of IgG2 could be a sign of poor prognosis in this population. Elevated levels of IgG4 may antagonise IgG2 helping to preserve relatively good pulmonary status.